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# Effects of Treatment on Morbidity in Hypertension

## Results in Patients With Diastolic Blood Pressures Averaging 115 Through 129 mm Hg

*Veterans Administration Cooperative Study Group on Antihypertensive Agents*

**A group of 143 male hypertensive patients with diastolic blood pressures (at the clinic) averaging between 115 and 129 mm Hg were randomly assigned to either active (hydrochlorothiazide plus reserpine plus hydralazine hydrochloride) or placebo treatment. Twenty-seven severe, complicating events developed in the placebo-treated patients as compared to two in the active group. Four deaths occurred in the placebo-treated group and none in the actively treated patients. Other complications in the placebo group included grade 3 or 4 hypertensive retinopathy, congestive heart failure, increasing azotemia, cerebrovascular thrombosis, transient ischemic attacks, cerebral hemorrhage, myocardial infarction, and severely elevated blood pressure. Severe complications in the active-treatment group were one cerebrovascular thrombosis and one case of multiple drug toxicity. Male patients with diastolic blood pressures averaging 115 mm Hg or above represent a high-risk group in which antihypertensive therapy exerts a significant beneficial effect.**

The value of antihypertensive drug treatment in malignant hypertension has been amply demonstrated.[1-6] However, its effectiveness in preventing morbidity and mortality in less severe forms of hypertension has been disputed.[7-9] Adequately controlled, prospective studies are needed to evaluate this question in patients with essential hypertension.[9] An investigation of this type was initiated by the Veterans Administration Cooperative Study Group on Antihypertensive Agents in 1963. The design of the study, including the precautions employed to maintain adherence to protocol and avoidance of dropouts, has been described in a previous communication.[10] The present report is concerned with the results obtained in the patients without signs of accelerated hypertension at admission whose diastolic blood pressures prior to treatment averaged 115 through 129 mm Hg.

For complete list of participants, see page 1033.

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### Plan of Investigation

All patients were hospitalized for the initial workup. Male patients whose diastolic blood pressures from the fourth through the sixth day of hospitalization averaged 90 through 129 mm Hg without treatment were considered for admission to the prerandomization trial period.

Severity was evaluated in five categories. These were the average diastolic blood pressure during hospitalization and the degree of clinically detectable hypertensive damage in the following four target organs: the optic fundi, the brain, heart, and kidneys. Severity of damage in each category was graded on a scale from 0 (no detectable abnormality) to 4 (most severe changes). The criteria used for grading severity have been described in detail elsewhere.[11] After doubling the scores for the average diastolic blood pressure and the severity of damage to the optic fundi, the scores obtained in each category were summed to obtain a total severity index. Patients with total scores of 2 through 7 were classified as mild, 8 through 15 as moderate, and 16 or above as severe, the latter being excluded from the trial.

Also excluded from the study were patients with surgically curable hypertension, uremia, and concomitant fatal diseases such as carcinoma. Patients with hemorrhages, exudates, or papilledema in the optic fundi, history of cerebral or subarachnoid hemorrhage, dissecting aneurysm, or congestive heart failure resistant to digitalis and mercurial diuretics were excluded. Additional exclusions included patients who wished to return to the care of their private physicians, those who for geographical or

other reasons would be unable to attend clinic regularly, and patients of dubious reliability such as alcoholics, vagrants, and poorly motivated patients.

*Prerandomization Trial Period.*—Following discharge from the hospital, the patients entered a prerandomization trial period of two to four months' duration. They received two placebos, known to the physician but not to the patient, and were seen in the clinic at monthly intervals.

Riboflavin (5 mg) was incorporated into one of the placebos. Riboflavin produces a yellow fluorescence of the urine when the latter is viewed under ultraviolet light. At each visit, a urine specimen was examined for fluorescence. Patients were required to return all bottles of medication, at which time the tablets were counted to assess the patient's reliability. To qualify for admission to the study, the patients were required to have no "violations" on two successive clinic visits. A violation consisted either of failure to appear at the regularly scheduled clinic appointment, or failure of the urine to exhibit fluorescence, or a tablet count (of either of the two types of placebos) which was outside the acceptable range. The upper limit of the acceptable range was defined as the return of no more than a 10% excess of the calculated number of tablets remaining if all doses had been taken as prescribed, while the lower limit was a return of five tablets less than the same calculated number. Nearly one half of the patients accepted into the trial period were excluded prior to randomization because of failure to pass the above tests of reliability.

Also excluded were patients who during the trial period exhibited diastolic blood pressures (while in the sitting position) averaging below 90 or above 129 mm Hg. Thus, the final decision to accept the patient into the study was based on both reliability and the level of diastolic blood pressure determined in the clinic during the trial period.

*Postrandomization Period.*—At the time of randomization, a sealed envelope was opened which assigned the patient to one of two possible regimens—active antihypertensive medications or their placebos. A table of random numbers was utilized by the statistician in determining the assignments. Patients classified by severity scores as having mild hypertension were randomized in a separate stratification from those with moderate hypertension. The double-blind technique was employed by utilizing a series of complex code numbers to disguise the identity of the randomized treatments and by making active drugs and placebos identical in appearance. It is realized, however, that blood pressure levels and side effects made the maintenance of such a double-blind study difficult and imperfect.

The active drugs were incorporated in the two tablets as follows: tablet A contained 50 mg hydrochlorothiazide plus 0.1 mg reserpine, and tablet B contained hydralazine hydrochloride. Tablet B was available in two strengths, 25 and 50 mg. Placebos were made up to correspond with each tablet of the active drugs.

Table 1.—Background of Randomized Patients

| Characteristic | No. Placebo Treated | No. Actively Treated |
|---|---|---|
| Total randomized | 70 | 73 |
| White | 35 | 31 |
| Negro | 35 | 42 |
| Family history of hypertension | | |
| None | 19 | 23 |
| Present | 48 | 49 |
| Unknown | 3 | 1 |
| Cardiac symptoms | | |
| None | 48 | 52 |
| Present | 22 | 21 |
| Heart size by roentgenogram | | |
| Ungerleider normal | 39 | 44 |
| Ungerleider enlarged | 31 | 29 |
| Electrocardiogram | | |
| Left ventricular hypertrophy absent | 48 | 49 |
| Left ventricular hypertrophy present | 22 | 24 |
| Prior cardiovascular thrombosis | 5 | 6 |
| Occipital headaches | 12 | 10 |
| Diabetes absent | 65 | 65 |
| Diabetes present | 5 | 8 |

Table 2.—Measurement Data

| Characteristic | Placebo Mean | Placebo SD | Active Mean | Active SD |
|---|---|---|---|---|
| Age (yr) | 51.4 | 10.8 | 50 | 8.7 |
| Height (in) | 69 | 2.6 | 68.7 | 2.9 |
| Weight (lb) | 182.9 | 34.5 | 185.2 | 36.7 |
| Duration known hypertension (yr) | 5.4 | 4.4 | 5.3 | 4.7 |
| Average hospital diastolic pressure (mm Hg) | 105.8 | 8.4 | 106.5 | 8.4 |
| Average clinic systolic (mm Hg) | 186.8 | 17.2 | 185.6 | 15.4 |
| Average clinic diastolic (mm Hg) | 121 | 4.7 | 121.2 | 5 |
| Severity grades (0-4)* | | | | |
| Fundi (hypertensive) | 1.2 | ... | 1.3 | ... |
| Fundi (sclerotic) | 1.3 | ... | 1.4 | ... |
| Cardiac | 1.2 | ... | 1 | ... |
| Central nervous system | 0.4 | ... | 0.3 | ... |
| Renal | 0.5 | ... | 0.3 | ... |
| Blood glucose, fasting (mg/100 cc) | 96.8 | 20.6 | 97.7 | 18.9 |
| Blood glucose, 2-hr postprandial | 118 | 41.5 | 116.1 | 54.3 |
| Cholesterol (mg/100 cc) | 251.3 | 59.5 | 242 | 51.5 |

*Detailed criteria for grades 0 through 4 are given in reference 11.

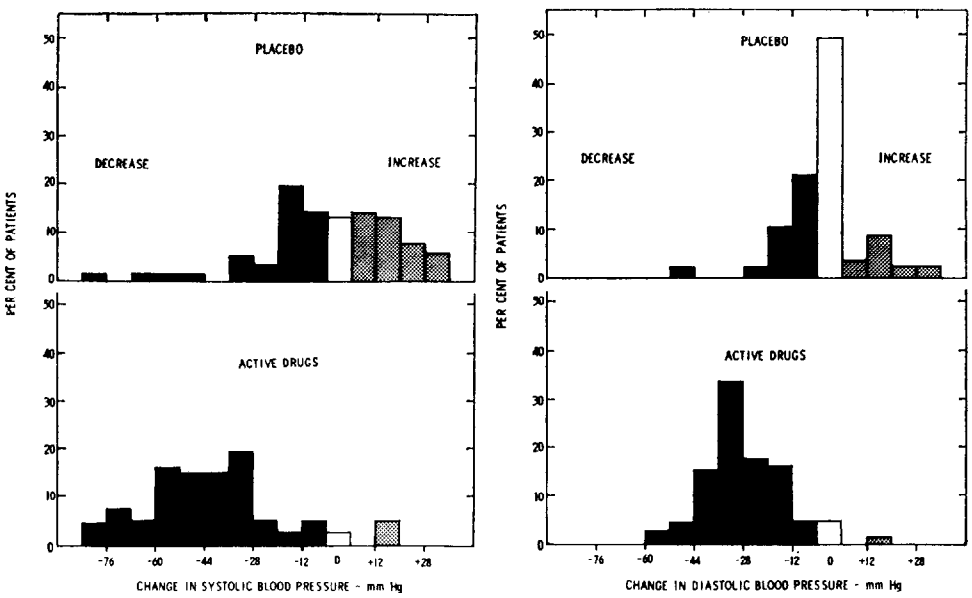
Table 3.—Trends of Diastolic Blood Pressure

| Time of Observation | Placebo No. Patients Observed* | Placebo Average Diastolic, mm Hg | Active No. Patients Observed | Active Average Diastolic, mm Hg |
|---|---|---|---|---|
| Prerandomization | 70 | 121 | 73 | 121.2 |
| At 4 months | 57 | 118.5 | 68 | 93.1 |
| 8 | 50 | 120.3 | 64 | 92.2 |
| 12 | 44 | 118.8 | 58 | 91.6 |
| 16 | 33 | 118.5 | 47 | 92.1 |
| 20 | 27 | 115.2 | 40 | 89.4 |
| 24 | 23 | 119.7 | 32 | 91.5 |

*The decline in the number of patients observed is due primarily to the fact that patients were admitted over a 2½-year period. Hence, many were not in the study long enough to be observed at the longer time periods.

Treatment was begun with either tablet A, one twice daily, plus the 25-mg tablet B, one tablet three times daily, or else with the placebos of both of these tablets. At the next visit, tablet B was increased to the 50-mg strength. Thus, the regular maintenance daily dose to patients randomized to the active regimen was 100 mg of hydrochlorothiazide, 0.2 mg of reserpine, and 150 mg of hydralazine hydrochloride. However, if there were hypotensive reactions or other severe side effects, doses could be reduced to a tolerable level.

In order to further minimize losses due to drug




**Changes in systolic (*left*) and diastolic blood pressure (*right*) after four months of treatment in 57 patients given placebos (*above*) and 68 patients treated with hydrochlorothiazide plus reserpine plus hydralazine (*below*).**

toxicity, two special A tablets were available on request. One contained hydrochlorothiazide without reserpine for patients becoming depressed or having active peptic ulcer or other reserpine-associated severe side effects. The other contained reserpine without hydrochlorothiazide for toxicity associated with the latter, such as hyperglycemia or acute gout. These special A tablets were available in both active and placebo forms.

The patients visited the clinic at monthly intervals for the first two months following randomization and at bimonthly intervals henceforth. Additional interim visits were scheduled if needed. Tablet counts were made at all clinic visits and fluorescence tests of the urine were made at alternate visits. Annual examinations included complete physical examination, roentgenogram of the chest, electrocardiogram, blood chemistry, and renal function tests. General medical care measures and symptomatic treatment, with the exception of known active antihypertensive drugs, were employed in all patients.

## Characteristics of Patients

Only the patients whose diastolic blood pressures averaged 115 to 129 mm Hg during the last two prerandomization clinic visits are included in the present report. For this high-risk group the study was ended in May 1967. The patients with lower prerandomization diastolic readings are continuing in the study and will be reported on later. The study was terminated in the 115 mm Hg and above group at an earlier date than expected when it became apparent that the risk rate increased sharply at these levels of diastolic blood pressure and that the clinical course of such patients appeared to be favorably influenced by antihypertensive drug treatment. Therefore, all patients in this high-risk group have since been given active treatment.

The total number of high-risk patients randomized was 143. Of this total, 70 received placebos, and 73 received active antihypertensive drugs during the randomization trial. Their average age was 51 years with a range of 30 to 73 years. The average weight was 83.5 kg (184 lb). Seventy-seven patients were Negroes and 66 whites. There were no significant differences with regard to age, weight, duration of known hypertension, or family history of hypertension, between the placebo- and active-treatment groups (Tables 1 and 2). There were more Negro and diabetic patients in the actively treated than in the placebo group, but the differences were not significant. The various indices of severity such as hospital and clinic blood pressure; funduscopic, cardiac, central nervous system, and renal abnormalities were essentially similar in the two groups.

The 143 patients were admitted into the study from April 1964 to December 1966. Observations on all these patients ended in May 1967. Thus, there is considerable variation in the duration of observation (Table 3). Nevertheless, 38% of the patients were observed for two years or more. The duration of the postrandomization phase of the study averaged 15.7 months for the placebo-treated patients and 20.7 for the active-drug group. Twenty-six of the placebo patients were in the postrandomization period of the study for less than one year as compared to 15 of the active group. Twenty-three placebo-treated patients exceeded a two-year period of postrandomization follow-up as opposed to 32 of the actively treated patients. The briefer period of follow-up of the patients in the placebo group was caused by the larger number of terminating events which developed in this group.

*Modification in Treatment Regimens.*—Of the 73

Table 4.—Incidence of Mortality and Morbidity

| | Placebo-Treated Patients | Actively Treated Patients |
|---|---|---|
| Deaths | 4 | 0 |
| Class A events | 10 | 0 |
| **Subtotal** | 14 | 0 |
| Other treatment failures | 7 | 1 |
| **Total terminating events** | 21 | 1 |
| Class B events (nonterminating) | 6 | 1 |
| **Total** | 27 | 2 |

patients randomized to active antihypertensive drugs, 45 received the standard maintenance doses of hydrochlorothiazide, 50 mg plus reserpine 0.1 mg twice daily, and hydralazine hydrochloride, 50 mg three times daily, throughout their participation in the study. Dosages were reduced in the remaining patients because of low blood pressure levels with the standard regimen or because of side effects such as severe headache or weakness. There were no cases of systemic lupus erythematosus. Two patients were transferred to the special A tablets, one because of depression and the other because of a hyperglycemic reaction.

Sixty-six of the 70 placebo-treated patients received standard maintenance dosages. Reduced doses of tablet B were given to two patients because of presumed hydralazine-induced side effects. Special tablet A placebos were substituted in two other patients because of depression.

*Dropouts.*—The total number of dropouts was 12 or 8.4%. Nine occurred during the first two months following randomization. Seven had been randomized to placebos and five to active drugs. Thus, the dropout rate was small and was approximately equally divided between the active- and placebo-treated patients.

*Changes in Blood Pressure.*—Systolic and diastolic blood pressures fell promptly and significantly in the actively treated patients and remained at these reduced levels throughout the trial. The prospective trends for diastolic blood pressure recorded with the patients in the sitting position are shown in Table 5. After 24 months of active treatment, the reduction from prerandomization levels of clinic blood pressure averages 43 mm Hg systolic and 29.7 mm Hg diastolic. By contrast, the placebo-treated patients showed no significant changes in average blood pressure levels following randomization (Table 3). The distribution of individual changes are shown in the Figure. There is a marked shift to the left into the "decrease" zone for the treated patients as compared with the placebo group. This marked shift is evident for both systolic and diastolic changes. Also apparent is the wide variation in individual responses.

## Assessable Morbid Events

As shown in Table 4 assessable morbid events occurred in 27 placebo-treated versus two actively treated patients. Using the chi-square test, and assuming that the treatment has no effect, this result is statistically significant at the $P<.001$ level. If the possible effect of the 12 patient dropouts is considered and the most adverse assumption made, namely, that the seven placebo-treated patients would have had no countable event if they had stayed in the study and the five patients taking active drugs each would have had a countable event (a most unlikely occurrence!), then the score would have been 27 to 7. But even this con-

Table 5.—Terminating Events

| No. | Age | Race | Prerandomized Blood Pressure, mm Hg | Time in Randomized Trial, Months | Class of Events* | Nature of Terminating Event |
|---|---|---|---|---|---|---|
| Placebo | | | | | | |
| 1 | 57 | W | 185/126 | 16 | A, D | Dissecting aortic aneurysm |
| 2 | 59 | W | 214/120 | 6 | A, D | Dissecting aortic aneurysm |
| 3 | 55 | N | 177/117 | 2 | B, D | Sudden death |
| 4 | 65 | W | 230/127 | 2 | B, D | Ruptured abdominal aortic aneurysm |
| 5 | 65 | N | 211/121 | 4 | A | Cerebral hemorrhage; bloody xanthrochromic spinal fluid |
| 6 | 49 | W | 192/123 | 24 | A | Fundi striate hemorrhage and papilledema |
| 7 | 69 | W | 225/123 | 12 | A | Fundi striate hemorrhage and papilledema |
| 8 | 53 | W | 180/122 | 2 | A | Fundi striate hemorrhage and soft exudates |
| 9 | 68 | W | 214/117 | 12 | A | Fundi striate hemorrhage and soft exudates |
| 10 | 37 | N | 211/122 | 8 | A | Fundi bilateral striate hemorrhage |
| 11 | 45 | N | 200/121 | 2 | A | Fundi bilateral striate hemorrhage and congestive heart failure |
| 12 | 50 | W | 180/118 | 17 | A | Fundi bilateral striate hemorrhage and congestive heart failure |
| 13 | 67 | N | 215/120 | 2 | A | Elevated BUN level to 71 mg/100 cc |
| 14 | 55 | W | 186/125 | 5 | A | Rehospitalization, basal diastolic pressure average 136 mm Hg |
| 15 | 46 | W | 170/125 | 10 | TF | Fundi single soft exudate |
| 16 | 53 | W | 196/128 | 24 | TF | Rehospitalization, basal diastolic pressure average 128 mm Hg |
| 17 | 69 | W | 188/116 | 24 | TF | Fundi hemorrhage and exudate but also diabetic |
| 18 | 44 | N | 193/127 | 16 | TF | Rehospitalization, basal diastolic pressure average 100 mm Hg |
| 19 | 68 | W | 197/121 | 26 | TF | Fundi hemorrhage and soft exudates plus BUN level 70 mg/100 cc but also diabetic |
| 20 | 34 | N | 165/117 | 13 | TF | Creatinine level increase 1.1 to 3 and BUN level 18 to 28 mg/100 cc in young patient |
| 21 | 60 | N | 205/115 | 4 | B, TF | Cerebrovascular accident, paralysis, and invalidism |
| Active | | | | | | |
| 22 | 47 | W | 167/118 | 7 | TF | Hyperglycemia, depression |

*A = class A event, D = death, TF = treatment failure, and B = class B event

Table 6.—Class B (Nonterminating) Events

| Patient No.* | Age | Race | Prerandom BP, mm Hg | Time in Trial, mo: Before Events | Time in Trial, mo: After Events | Nature of Events |
|---|---|---|---|---|---|---|
| 1 | 48 | W | 182/117 | 4 | 24 | Myocardial infarction |
| 2 | 45 | N | 165/115 | 18 | 10 | Myocardial infarction |
| 3 | 46 | W | 175/121 | 11 | 9 | Congestive heart failure |
| 4 | 68 | W | 180/120 | 20 | 9 | Congestive heart failure |
| 5 | 59 | N | 217/119 | 2 | 4 | Cerebrovascular thrombosis |
| 6 | 45 | W | 181/120 | 5† | 15 | Transient ischemic attacks |
| 7 | 66 | W | 188/124 | 1 | 26 | Cerebrovascular thrombosis |

*Patients 1 through 6 received placebos; patient 7 received active therapy.
†Subsequent ischemic attacks at 13 and 15 months after randomization.

servative hypothetical "result" is statistically significant at the .001 level.

When deaths and class A hypertensive complications are combined, such events occurred in 14 placebo-treated patients as compared to none in the group receiving antihypertensive drugs. The total number of patients with terminating events, which includes deaths, class A events, and other treatment failures, was 21 in the placebo group versus one in the actively treated group.

*Terminating Events in Placebo-Treated Patients.*—The 21 placebo-treated patients having complications which required discontinuation of the protocol assigned treatment are listed in Table 5. The average age of these patients was 55.2 years, which was four years older than the average age of the total randomized population. Thirteen of the terminating events occurred in whites and eight in Negroes. The average clinic blood pressure of the 21 patients prior to randomization was 196.9/121.5 mm Hg, a slightly higher systolic average than that found in the entire group at risk.

The shortest period from randomization to terminating event was 2 months, the longest 26 months and the average 11 months. Terminating events were well distributed among the 15 participating hospitals, 14 contributing one or more events.

1. *There were four deaths,* all of which were related to cardiovascular diseases. Dissecting aortic aneurysm occurred in two, ruptured abdominal aneurysm in one, and sudden death at home in one (Table 5). No autopsy was obtained in the latter instance. The diagnosis of dissecting aortic aneurysm was verified either at surgical exploration or at autopsy. The diagnosis of ruptured abdominal aortic aneurysm with fatal hemorrhage was verified at autopsy.

2. *Class A events* were those hypertensive complications as defined in the protocol which required treatment with known active agents and permanent removal from protocol assigned therapy. They included the following: funduscopic evidence of grade 3 or 4 hypertensive retinopathy (multiple striate hemorrhages or soft exudates in more than one quadrant, or bilateral papilledema), doubling of blood urea nitrogen (BUN) to levels above 60 mg/100 cc; dissecting aortic aneurysm; cerebrovascular hemorrhage as opposed to thrombosis; subarachnoid hemorrhage; congestive heart failure persisting despite digitalis and mercurial diuretics; and elevation of diastolic blood pressures to 140 mm Hg or higher on three repeated visits and average rehospitalization diastolic pressure to 130 mm Hg or higher.

The case histories of patients having terminating events were reviewed by a panel of four members consisting of two participants and two consultants. The panel determined in each case whether the criteria for a class A event as defined in the protocol were fulfilled. Terminating events which did not fully meet these criteria were classified as treatment failures as described below.

There were ten class A events in which the patients lived. Two of these were considered irreversible, and eight proved to be reversible following active antihypertensive treatment. One of the irreversible events was a cerebrovascular hemorrhage as evidenced by hemiplegia, stiff neck, and bloody and xanthrochromic spinal fluid. The other occurred in an azotemic patient whose renal function deteriorated rapidly.

Seven of the eight reversible class A events included grade 3 or 4 changes in the optic fundi. In two, striate hemorrhages and papilledema were present. In two others, multiple bilateral striate hemorrhages and cotton wool exudates were visualized; in two additional patients bilateral striate hemorrhages and resistant congestive heart failure were present simultaneously; and in the seventh patient, striate hemorrhages were present bilaterally but without exudates (Table 5). The remaining reversible class A event was associated with severely elevated blood pressure, the diastolic pressure during rehospitalization averaging 136 mm Hg.

3. *Treatment failures* were those events which did not meet the specific criteria for any one class A event as defined in the protocol. Nevertheless, because the complications were considered to be life threatening, protocol drugs were removed and treatment instituted with known antihypertensive agents. Seven of the terminated placebo-treated patients were classified as treatment failures. In two, multiple striate hemorrhages and soft exudates were seen in the optic fundi, but these patients also had diabetes mellitus. That the retinopathy probably was primarily associated with hypertension is suggested by the fact that, in both instances, the changes in the fundi cleared within two months after initiation of treatment with known antihypertensive agents. In a third nondiabetic patient only one cotton wool exudate and no striate hemorrhages were observed.

Two patients were classified as treatment failures because the diastolic blood pressures in the clinic were frequently recorded above 140 mm Hg but averaged below 130 mm Hg during rehospitaliza-

tion. Additionally, a 34-year-old patient was removed from protocol therapy because previously normal levels of BUN and serum creatinine increased to 28 and 3 mg/100 cc respectively at the time of annual examination. The final treatment failure was a cerebrovascular accident diagnosed as thrombosis rather than hemorrhage, but which resulted in complete invalidism and inability to return to the clinic.

*Terminating Event in Actively Treated Patients.*—The single terminating events in the 73 patients who received active drugs occurred in a patient with multiple drug toxicity. Five months before termination the patient was found to have a blood glucose level of 450 mg/100 cc and a serum potassium value of 2.5 mEq/liter. Both abnormalities disappeared when the special A tablet containing only reserpine was substituted. However, five months later he had a mental depression.

*Nonterminating (Class B) Morbid Events.*—Class B events (Table 6), as opposed to class A events, were those which did not require permanent discontinuation of protocol treatments. Patients with developing B events could be treated with known antihypertensive agents for as long as six months, after which, protocol treatment had to be reinstituted. Class B events included organic complications associated with atherosclerosis, such as cerebrovascular thrombosis (as constrasted to hemorrhage which was considered a class A event) or myocardial infarction. Congestive heart failure which responded to routine therapy with digitalis or mercurials and did not require antihypertensive agents also was classified as a B event.

Seven patients, in addition to those described above under terminating events, had class B complications during the course of the trial (Table 6). These events occurred in six placebo-treated patients and in one actively treated. In the placebo-treated group myocardial infarction accompanied by diagnostic electrocardiographic and serum transaminase changes occurred in two patients. Congestive heart failure occurred in two others, the symptoms and signs of which cleared following treatment with digitalis. Cerebrovascular thrombosis was diagnosed in the fifth case, and the sixth had repeated transient episodes of left-sided hemiparesis. The single class B event in the active-treatment group occurred in a 68-year-old man who had hypotensive levels of blood pressure accompanied by a left-sided hemiparesis.

## Comment

Although essential hypertension is generally regarded as a slowly progressive disorder, such did not appear to be the case in these male patients with clinic diastolic blood pressures of 115 mm Hg or higher. An extremely high incidence of severe complications, especially early funduscopic manifestations of accelerated hypertension occurred in the placebo-treated group. A similar high incidence of severe hypertensive complications occurring in placebo-treated patients over a two-year period of observation was reported by Wolff and Lindeman.[12] They attributed this in part to the fact that their clinic population was primarily a lower-income Negro group. However, in the present report more whites than Negroes had hypertensive complications despite equal numbers of each race randomized to placebos.

The majority of prior reports on the effects of antihypertensive drug treatment in essential hypertension have not contained randomized control groups. Hodge et al[13] utilized as their control the patients who refused to undertake treatment. They found a 50% reduction in mortality in the treated group over a period of 1 to 8 years of observation in patients with grade 2 hypertensive retinopathy. Leishman's untreated patients were those who declined or who were considered unsuitable for sympathectomy.[14] He found morbidity and mortality reduced by two thirds in the treated group. Hood and his associates[15] using a nonrandomized untreated control group concluded that mortality was considerably reduced by treatment in essential hypertension.

A prospective, randomized control study was carried out by Wolff and Lindeman in 87 patients.[12] Twelve percent defaulted. Over a two-year period the incidence or morbid events in the treated patients was one third of that observed in the placebo group. Hamilton[16] alternately assigned 61 patients with clinic diastolic blood pressures averaging 110 mm Hg or higher to active treatment and placebo. Thirty were treated with antihypertensive agents and 31 were not. Over an eight-year period of follow-up, 16 of the untreated patients had complications, primarily strokes, as compared to five of the treated group. Of the latter, four exhibited poor blood pressure control. If they are excluded, only one of the treated patients had a severe complication.

The evidence provided by these earlier studies plus the present report leaves little doubt as to the value of antihypertensive drug therapy in essential hypertension associated with clinic diastolic blood pressures of 115 mm Hg or more. It appears that the majority of such patients can be managed satisfactorily with combinations of thiazides, reserpine, and hydralazine,[17] none of which require more than minor dosage adjustments.

### Generic and Trade Names of Drugs

Hydralazine hydrochloride—*Apresoline Hydrochloride.*
Hydrochlorothiazide—*Aquarius, Esidrix, Hydril, Hydrodiuril, Oretic.*
Reserpine—*Rauloydin, Raurine, Rau-Sed, Reserpoid, Sandril, Serfin, Serpasil, Serpate, Vio-Serpine.*

### Participants

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Overbeck, MD; Eliseo C. Perez-Stable, MD; Eli A. Ramirez, MD; and J. R. Thomas, MD.

**Participating Veterans Administration Hospitals:** Bronx; Brooklyn; Dearborn, Mich; Iowa City; Jackson, Miss; Memphis; Nashville; Oklahoma City; Pittsburgh; Richmond, Va; Salt Lake City; San Juan, PR; Washington, DC; West Haven, Conn; and West Roxbury, Mass.

**Biostatisticians:** Russell B. Tewksbury, ScD, and Lawrence W. Shaw.

**Consultants and Associates:** Walter M. Kirkendall, MD; David W. Richardson, MD; and Louis Lasagna, MD.

The special medications used in this investigation were prepared by William E. Wagner, MD, of Ciba Pharmaceutical Co., Summit, NJ.

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